Imaging of atherosclerosis: magnetic resonance imaging

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Abstract: Atherosclerosis and its thrombotic complications are the major cause of morbidity and mortality in the industrialized countries. Despite advances in our understanding of the pathophysiology, pathogenesis, and new treatment modalities, the absence of an adequate non-invasive imaging tool for early detection limits both the prevention and treatment of patients with various degrees and anatomical localizations of atherothrombotic disease. An ideal clinical imaging modality for atherosclerotic vascular disease should be safe, inexpensive, non-invasive or minimally invasive, accurate, and reproducible, and the results should correlate with the extent of atherosclerotic disease and have high predictive values for future clinical events. High-resolution magnetic resonance imaging (MRI) has emerged as the most promising technique for studying atherothrombotic disease in humans in vivo. Most importantly, MRI allows for the characterization of plaque composition, i.e. the discrimination of lipid core, fibrosis, calcification, and intraplaque haemorrhage deposits. Magnetic resonance imaging also allows for the detection of arterial thrombi and in defining thrombus age. Magnetic resonance imaging has been used to monitor plaque progression and regression in several animal models of atherosclerosis and in humans. Emerging MRI techniques capable of imaging biological processes, including inflammation, neovascularization, and mechanical forces, may aid in advancing our understanding of the atherothrombotic disease. Advances in diagnosis do prosper provided they march hand-in-hand with advances in treatment. We stand at the threshold of accurate non-invasive assessment of atherosclerosis. Thus, MRI opens new strategies ranging from screening of high-risk patients for early detection and treatment as well as monitoring of the target lesions for pharmacological intervention. Identification of subclinical atherosclerosis and early treatment initiation has the potential to surpass conventional risk factor assessment and management in terms of overall impact on cardiovascular morbidity and mortality. Such strategy is currently under clinical investigation

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REVIEW

Imaging

Imaging of atherosclerosis: magnetic resonance imaging

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Atherosclerosis and its thrombotic complications are the major cause of morbidity and mortality in the industrialized countries. Despite advances in our understanding of the pathophysiology, pathogenesis, and new treatment modalities, the absence of an adequate non-invasive imaging tool for early detection limits both the prevention and treatment of patients with various degrees and anatomical localizations of atherothrombotic disease. An ideal clinical imaging modality for atherosclerotic vascular disease should be safe, inexpensive, non-invasive or minimally invasive, accurate, and reproducible, and the results should correlate with the extent of atherosclerotic disease and have high predictive values for future clinical events. High-resolution magnetic resonance imaging (MRI) has emerged as the most promising technique for studying atherothrombotic disease in humans *in vivo*. Most importantly, MRI allows for the characterization of plaque composition, i.e. the discrimination of lipid core, fibrosis, calcification, and intraplaque haemorrhage deposits. Magnetic resonance imaging also allows for the detection of arterial thrombi and in defining thrombus age. Magnetic resonance imaging has been used to monitor plaque progression and regression in several animal models of atherosclerosis and in humans. Emerging MRI techniques capable of imaging biological processes, including inflammation, neovascularization, and mechanical forces, may aid in advancing our understanding of the atherothrombotic disease. Advances in diagnosis do prosper provided they march hand-in-hand with advances in treatment. We stand at the threshold of accurate non-invasive assessment of atherosclerosis. Thus, MRI opens new strategies ranging from screening of high-risk patients for early detection and treatment as well as monitoring of the target lesions for pharmacological intervention. Identification of subclinical atherosclerosis and early treatment initiation has the potential to surpass conventional risk factor assessment and management in terms of overall impact on cardiovascular morbidity and mortality. Such strategy is currently under clinical investigation.

Keywords Arteriosclerosis • Plaques • Magnetic resonance • Imaging • Therapy

Introduction

Atherothrombosis is a systemic arterial disease mainly involving the intima of large- and medium-sized systemic arteries, most commonly the carotid, aorta, coronary, and peripheral arteries. The main components of the atherothrombotic plaques are: (i) connective tissue extracellular matrix, including collagen, proteoglycans, fibronectin, and elastic fibres; (ii) crystalline cholesterol, cholesteryl esters, and phospholipids; (iii) cells such as monocyte-derived macrophages, T-lymphocytes, and smooth muscle cells, and eventually (iv) thrombotic material with platelets and fibrin. Varying proportions of these components occur in different plaques, thus giving rise to a heterogeneity of lesions.[1–3] These components mainly affect the intima within the subendothelial space, but secondary changes also occur in the media and adventitia,[4] particularly the growth of vasa vasorum.[5] Exemplifying the heterogeneity of lesions, disruption-prone plaques in the coronary arteries, the so-called high-risk or 'vulnerable plaques', tend to have a thin fibrous cap (cap thickness <65 μm), a large lipid core ($>40\%$ of the total lesion area), and a high degree of inflammation.[1,6,7] In contrast, carotid artery plaques prone to rupture are severely stenotic and predominantly fibrotic.[8] Since the composition of the 'high-risk plaques' varies depending on their anatomical site, with striking heterogeneity even within the same individual, reliable non-invasive imaging modalities able to detect and characterize atherothrombotic disease in its various stages and their different anatomical regions are clinically desirable.[9] Such imaging modalities would improve our understanding of the pathophysiological mechanisms underlying the atherothrombotic processes and allow for better risk stratification of the overall 'burden' of disease. Additionally, such tools may permit optimal tailoring of treatment and allow direct monitoring of the vascular response.[10]

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Techniques such as magnetic resonance imaging (MRI) are critical for the development of novel therapeutics as they allow for precise monitoring of the treatment effects over time. Advances in diagnosis therefore prosper when they march hand-in-hand with advances in treatment. Today, we stand at the threshold of accurate non-invasive assessment of atherosclerosis. Identification of subclinical atherosclerosis and early treatment initiation has the potential to surpass conventional risk factor assessment and management in terms of overall impact on cardiovascular morbidity and mortality. Such a strategy is currently under clinical investigation in the High-Risk Plaque Bioimaging Study in which novel approaches are tested in a typical health-plan population.[11] This study has recruited 6000 active subjects and 1300 controls, of which a large proportion underwent non-invasive imaging [including ultrasound, computed tomography (CT), positron emission tomography (PET) and MRI] and are being followed for clinical events and resource use up to 3 years.

The aim of the present article is to provide an overview of the feasibility and validation data, as well as the research and clinical application of MRI to study atherosclerotic plaques.

Imaging of atherosclerosis

The assessment of atherosclerotic plaque burden by non-invasive imaging techniques should allow for early detection of the disease and *in vivo* identification of high-risk plaques.[10,12,13] Several invasive and non-invasive imaging techniques are available with which atherosclerotic disease can be assessed.[13] The angiogram, using X-ray technology as does CT, or MR, all provide excellent spatial resolution allowing to detect the presence of stenosis, the degree of luminal narrowing, and/or information of the luminal surface of protruding atherothrombotic disease. The use of non-invasive angiography techniques, with intravenous injection of a contrast agent, has become a routine clinical practice at many centres to outline the degree of stenosis of the carotid, renal, and peripheral arteries, and the aorta. Importantly, however, as plaques may be displaced outward, due to the so-called positive remodelling, the luminal diameter may appear normal despite significant disease.[14] Today, the goal of visualizing and characterizing the diseased arterial wall in patients has become a reality with the use of several imaging techniques. Invasive techniques such as intravascular ultrasound (IVUS) and IVUS-derived techniques (such as palpography, elastography, and virtual histology) can assess arterial remodelling, plaque characteristics of coronary arteries, and optical coherence tomography allows 'near-histological' resolution of plaque surface, providing crucial morphological information, and is currently standard in clinical research. Such techniques, once adequately validated, might potentially help to define the vulnerability of coronary atherosclerotic plaques.

High-resolution MRI has emerged as the leading non-invasive *in vivo* imaging modality for atherosclerotic plaque characterization. Magnetic resonance imaging does not involve ionizing radiation and can provide high-resolution images of multiple vascular territories. The MR image is based on the radiofrequency signal, typically from water protons, following administration of a radiofrequency pulse, while the subject is placed in a strong magnetic field. The emitted signal varies according to the water concentration and the relaxation times (T1 and T2). Using combined analysis of different tissue signal intensities generated by the application of T1-weigted (T1W), T2-weigted (T2W), and proton-density-weighted (PDW) images, it has been possible to determine both plaque anatomy and composition.[15] Thus, MRI differentiates plaque components on the basis of biophysical and biochemical parameters such as chemical composition, water content, physical state, molecular motion, or diffusion. Magnetic resonance imaging provides imaging without ionizing radiation and can be repeated sequentially over time.

Atherosclerotic plaque characterization by MRI is based on the signal intensities and morphological appearance of the plaque on multiple different contrast weighting. The key advantage of MRI is the opportunity to acquire and combine multicontrast images, both bright blood (such as time-of-flight, TOF) and black blood (such as T1W, T2W, and PDW with blood-flow suppression) to distinguish tissue composition within the atherosclerotic vessel wall.[9,16] High-resolution contrast weighting MRI has been used for *in vivo* assessment of atherosclerotic plaques in the human carotids (*Figure 1*),[9,16–18] aortic,[9,19] peripheral,[20,21] and coronary arterial disease.[22–24]

Feasibility and validation studies for plaque imaging using magnetic resonance imaging

The assessment of both the anatomy and composition of atherosclerotic plaques by MRI has been extensively validated in experimental models and in humans. Validation studies were initially performed in experimental models of atherosclerosis such as in cholesterol-fed rabbits[25,26] and pigs using clinically available MRI scanners and in mice[27] using high-field-strength MRI scanners. Worthley *et al*. were the first validating the MR technique for coronary plaque imaging *ex vivo*[28] and *in vivo*[22] in a clinical MRI scanner using a porcine model. In humans, validation was initially performed *ex vivo* using histological specimens[29,30] and subsequently *in vivo* in patients scheduled for carotid endarterectomy[16,18,31–35] or before surgical grafting of abdominal aortic aneurysm,[36] in which *in vivo* MR images were compared with histology.

Measurement of plaque size

Yuan and his group did extensive validation work on the carotid plaques. They were the first assessing the accuracy of vessel wall measurement using carotid high-resolution MRI in patients scheduled for endarterectomy.[18] The carotid lesions were excised *en bloc* and scanned again using similar imaging parameters. The paired *in vivo* and *ex vivo* measurements strongly agreed on the mean difference (*in vivo* minus *ex vivo*) in vessel wall area (VWA). Intra and inter-observer variability was small, with intraclass correlation coefficients ranging from 0.90 to 0.98. They concluded that MRI is highly accurate for *in vivo* measurement of VWA in atherosclerotic carotid lesions. This study showed for the first time that this imaging technique has potential application in monitoring lesion size in studies examining plaque progression and regression. We reported similar *in vivo* reproducibility data for VWA measurement by repeated MRI of the carotid arteries and thoracic aorta.[37] The image-specific error (standard deviation between matched image) was 6 mm^2 for aortic and 2 mm^2 for carotid images.

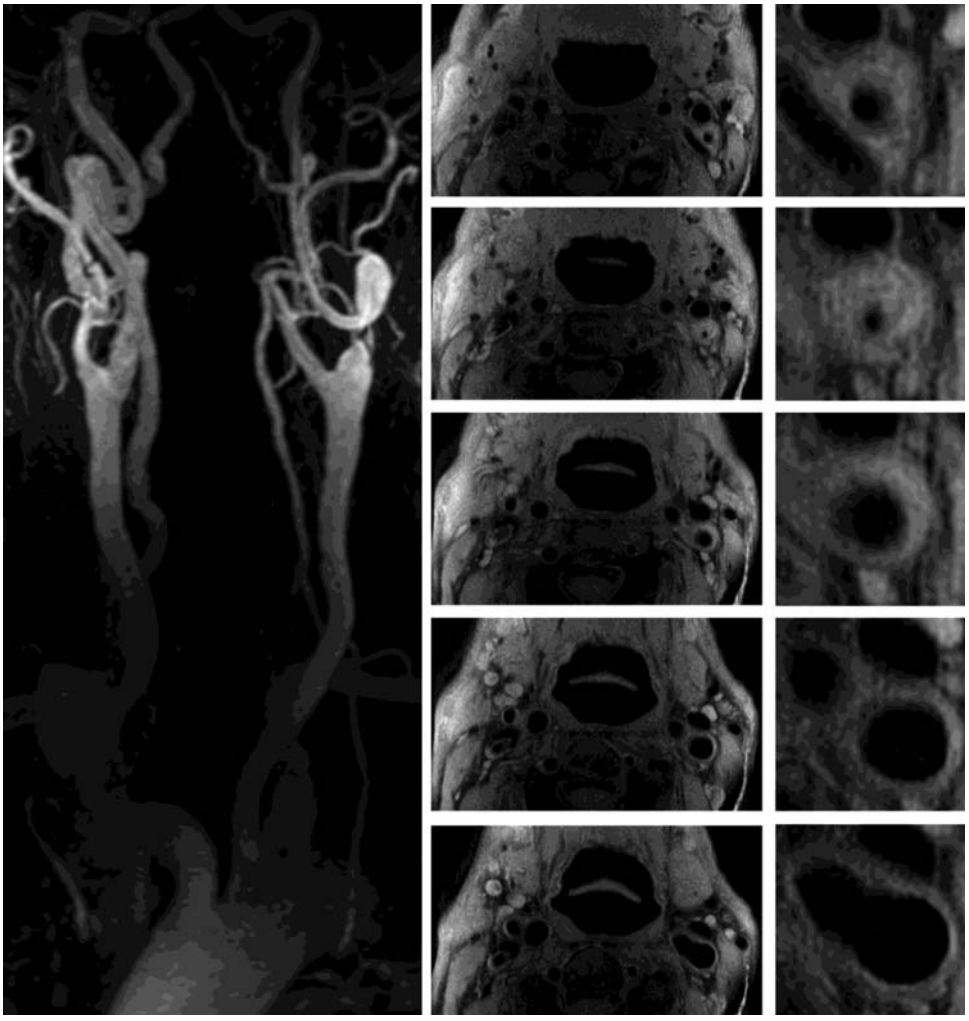

Figure 1 Magnetic resonance imaging of the carotid artery in a patient with arterial hypertension. The angiography with intravenous injection of gadolinium demonstrates a subtotal stenosis of the left carotid artery followed by a 360° loop due to the elongation of the artery. High-resolution magnetic resonance imaging allows visualization of the extension of the atherosclerotic plaque and anatomical distribution in relation to the surrounding structures.[9]

By averaging the values of five-contiguous images, the error was reduced to 4.5 mm^2 for aortic and 1.5 mm^2 for carotid images, corresponding to an error of 2.6% for aortic and 3.5% for carotid plaques. On the basis of these reproducibility data, changes in plaque size of >5% for aortic and >7% for carotid lesions are likely to be accurately measured by MRI.

Fayad *et al.*[19] assessed the atherosclerosis of the thoracic aorta by MRI and transoesophageal echocardiography (TEE)[38] and showed a strong correlation for plaque composition and mean maximum plaque thickness. Overall aortic plaque extent as assessed by TEE and MR was also statistically significant.

Assessment of plaque composition

In vivo assessment of plaque composition was initially performed in small animals such as rabbit[25,26] and mice.[27] Images were acquired *in vivo* and then correlated with the fine structure of the atherosclerotic lesions, including the fibrous cap, necrotic core, and lesion fissures, as verified by gross examination, dissection microscopy, and histology. In genetically engineered mice, excellent agreement between high-field MR and histopathology in grading of lesion shape and type was demonstrated.[27] Similar results have been described in the rabbit model using clinical MR scans.[25] Magnetic resonance imaging was performed in a 1.5 T system 9 months after induction of aortic atherosclerotic lesions, and the images were compared with matched histopathological sections.[25] A significant correlation was observed for mean wall thickness ($r = 0.87$), VWA ($r = 0.85$), and for plaque composition for the analysis of lipid rich (low signal on T2W, $r = 0.81$) and fibrous (high signal on T2W, $r = 0.86$) areas between MRI and histopathology. These studies indicated that serial analysis of therapeutic strategies on atherosclerotic plaque stabilization is feasible. Non-invasive high-resolution MRI has therefore demonstrated the potential

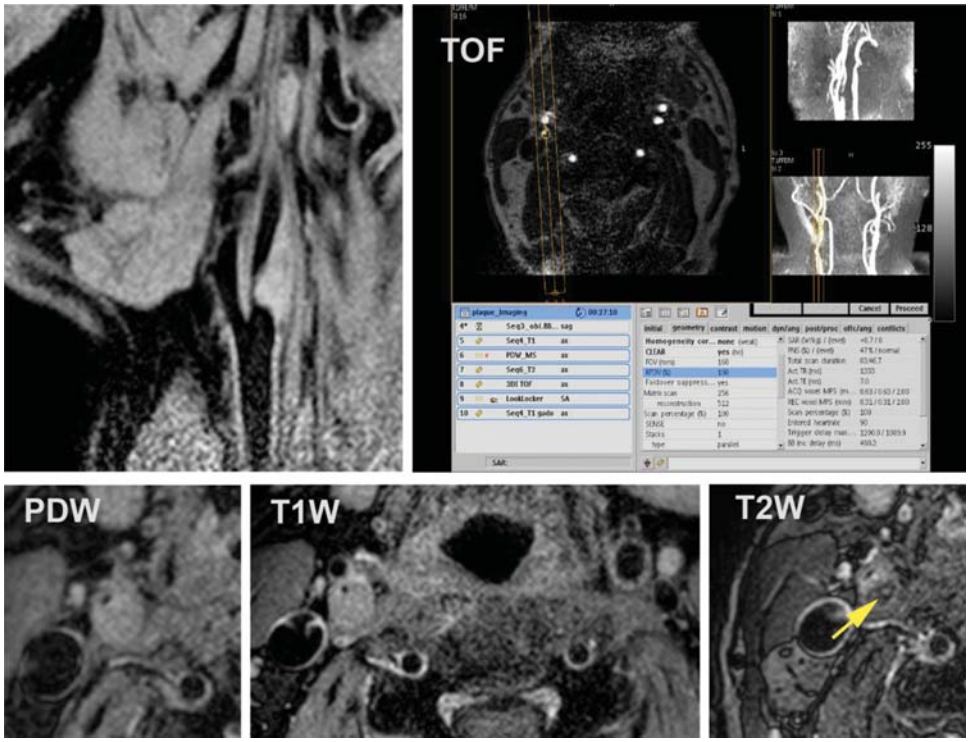

Figure 2 Magnetic resonance imaging examination of carotid atherosclerotic plaque in a patient with symptomatic carotid disease. An echo sequence is used to localize the carotid bifurcation (upper panel, left) and time-of-flight (TOF) sequence allows the definition of the stenosis without needing contrast injection (upper panel, right). Multisequence high-resolution magnetic resonance demonstrates the presence of a severely stenotic plaque with a large lipid core (yellow arrow in T2W image) (published with the permission of Prof. Dr A. Gallino and Dr R. Wyttenbach, Bellinzona, Switzerland).

to be applied *in vivo* as has been demonstrated by *ex vivo* experiments in the animal model.

In the validation of novel imaging techniques, it is essential to be able to bridge from pre-clinical models to humans. This was the case for MRI: in fact, several investigators used endarterectomy specimens to validate this technique in human first using *ex vivo* and then *in vivo* study design by imaging the patients *in vivo* before endarterectomy. Soila *et al.*[39] and Maynor *et al.*[40] have demonstrated that lipid components of atherosclerotic plaque could be distinguished with MRI. Toussaint *et al.*[29–31,41] showed that MRI was useful for the identification of fibrous cap characteristics. They found that calcification, fibrous intimal tissue, and intraplaque haemorrhage could be identified based on T2 measurements of carotid plaques *in vivo*.[29–31,41]

Although these images may still appear difficult to interpret to the reader who is not an expert, improvement in the technology is rapidly occurring and may one day be seen as the key technology to learn more about the mechanisms leading to atherosclerotic progression.

Assessment of atherosclerotic carotid artery plaques

The carotid arteries' superficial location (*Figure 1*) and relative absence of motion make them more suitable for MRI studies than do vessels such as the aorta or particularly the coronary arteries. Some of the carotid plaque MRI studies attempted both imaging and characterization of normal and pathological arterial walls,[31] the quantification of plaque size,[18] and the detection of fibrous cap integrity.[42] Magnetic resonance angiography can be combined with multicontrast, high-resolution black-blood spin-echo MRI sequences. Magnetic resonance angiography provides information on the severity of stenotic lesions and their spatial distribution, whereas the high-resolution black-blood sequences allow the characterization of plaque composition (*Figure 2*). This strategy may potentially allow patient risk stratification and selection of the adequate treatment modality.[9]

A strong association between fibrous cap thinning or rupture, as determined by MRI vessel wall TOF imaging, and the history of recent TIA or stroke was demonstrated (*Figure 3*).[17] The association between the presence of carotid intraplaque haemorrhage and neurological events was first described in endarterectomy specimens.[43] Intraplaque haemorrhage and fibrous cap disruption have been then documented *in vivo* by MRI in patients with symptomatic carotid stenosis.[17,44,45] High-intensity signals can be highly suggestive of complicated plaque by using specific magnetic resonance sequences designed for direct thrombus imaging (*Figure 4*). The prevalence of high signal was significantly greater in the patients' symptom-related ipsilateral vessels compared with the contralateral, asymptomatic side (60 vs. 36%, χ^2 $P < 0.001$),

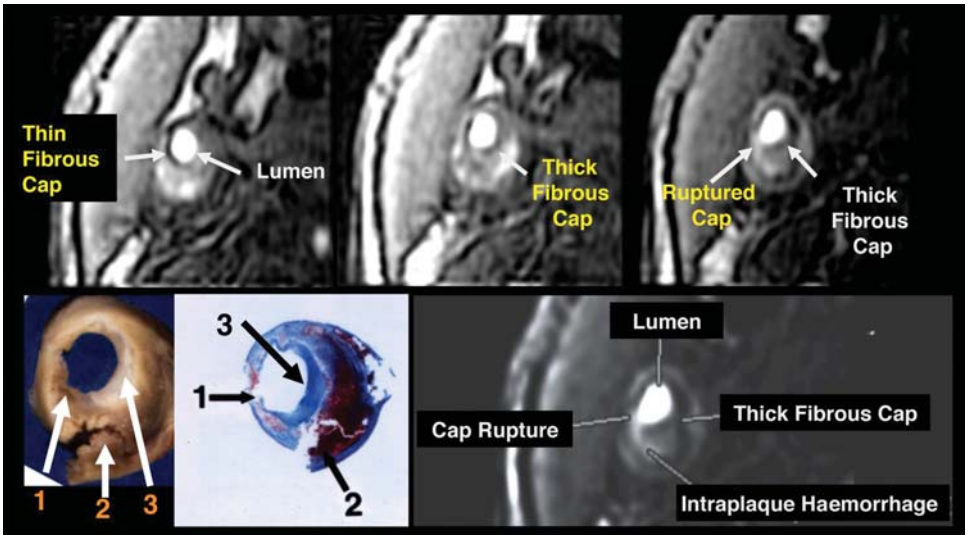

Figure 3 Magnetic resonance sequences normally used to perform angiography without the need of contrast agent (time-of-flight) allow the *in vivo* visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque. Gross and histological sections (lower left panel) showing the area of cap rupture (arrow 1) covering the recent intraplaque haemorrhage (arrow 2) and next to a region where fibrous cap is thick (arrow 3) (modified with permission from Yuan *et al.*[17] and Hatsukami *et al.*[42]).

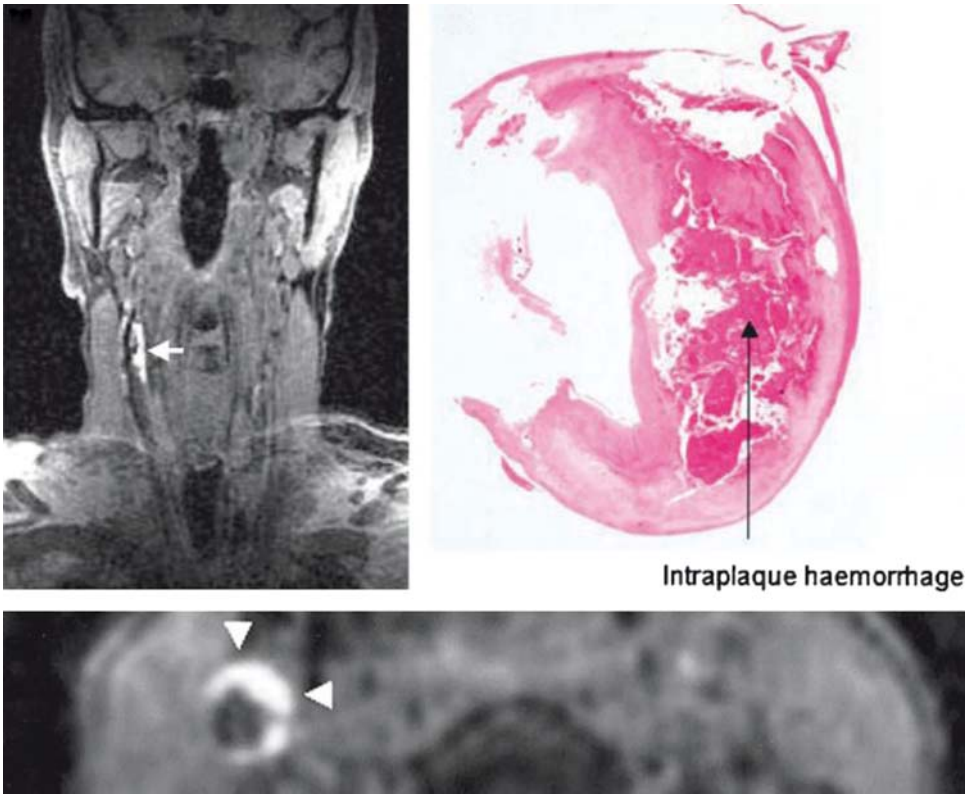

Figure 4 Specific designed sequences for the visualization of thrombi allow detection of intraplaque haemorrhage (arrow) in stroke patients (modified with permission from Moody *et al.*[76]).

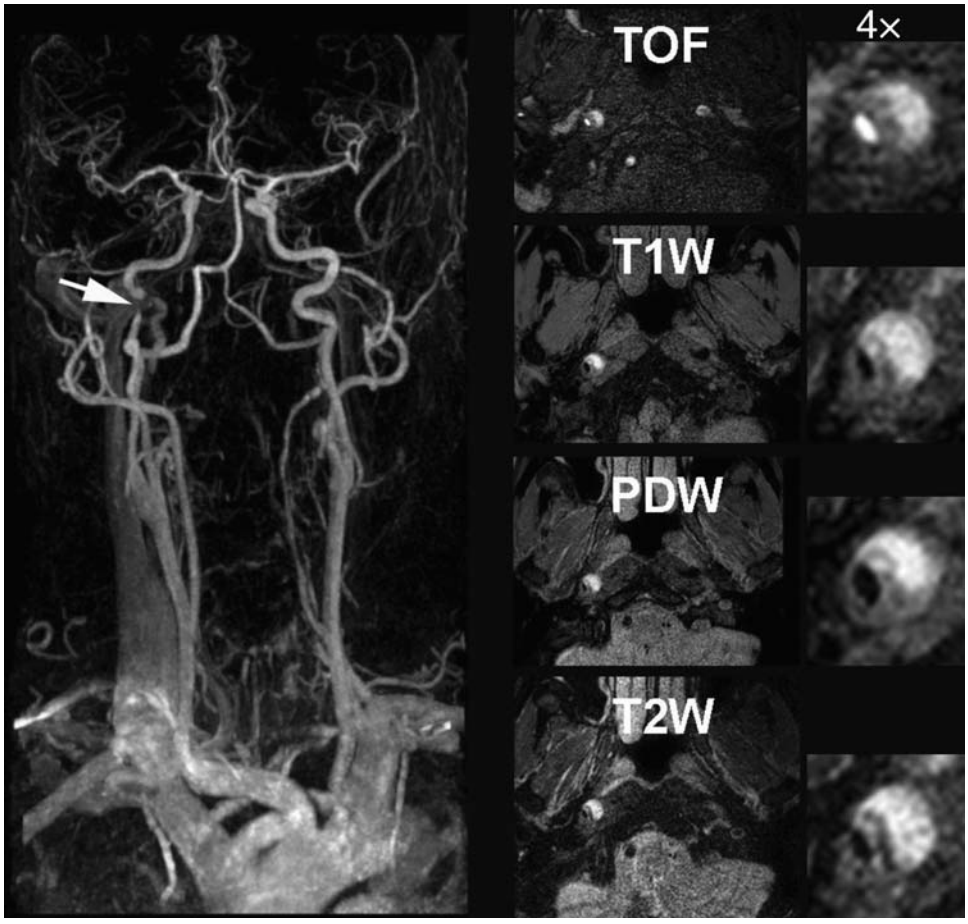

Figure 5 Magnetic resonance angiography demonstrating a subtotal stenosis of the right internal carotid artery (arrow) in a patient with acute stroke. High-resolution multicontrast imaging demonstrates a disrupted plaque with intraplaque haemorrhage as a cause of the subtotal obstruction (middle panels). Details of the cross-sectional multicontrast magnetic resonance images (four-fold enlargement) are provided in the right panels (published with the permission of Prof. Dr A. Gallino and Dr R. Wyttenbach, Bellinzona, Switzerland).

particularly for vessels of only moderate stenosis.[46] The prevalence of AHA type VI carotid lesions (presenting luminal surface defect, haemorrhage/thrombus, or calcified nodules) has been studied *in vivo* using MRI in patients ($n = 192$) with a different degree of carotid stenosis.[47] Lipid-rich necrotic core increased substantially with a higher degree of stenosis. Significant negative correlation between the minimum lumen area and complicated AHA type VI plaques was found. In fact, 92% of all patients with high-degree stenosis (80–99% luminal narrowing) had a lesion with lipid-rich necrotic core. Furthermore, the complicated AHA type VI positively correlated with the maximum wall area.

More recently, using 3 T MRI, it has been shown that intraplaque haemorrhage and large lipid-rich core are independently associated with thin or ruptured fibrous caps in patients with $\geq$50% carotid stenosis.[48]

Underhill *et al.*[49] recently provided prospective evidence that intraplaque haemorrhage could be a driving force behind luminal obstruction and, therefore, could be a potential mechanistic explanation for rapid plaque progression. Neovasculature, principally arising from the vasa vasorum as a consequence of inflammation-induced angiogenesis, has been implicated in the aetiology of intraplaque haemorrhage. Indeed, the newly formed vessels within plaques appear particularly prone to rupture. Thus, given the impact of neovasculature on disease progression, the opportunity to provide *in vivo* imaging of these structures to provide new mechanistic insights is particularly appealing.[50,51]

In patients with acute stroke, high-resolution MRI has therefore the potential of providing the essential information on the cause of vessel obstruction, differentiating between thrombo-embolic occlusion, plaque rupture, or dissection (*Figure 5*).

Assessment of aortic plaques

The principal challenges associated with MRI of the thoracic aorta are obtaining sufficient sensitivity for submillimetre imaging and exclusion of artifacts due to respiratory motion and pulsatile changes due to the blood flow. These challenges have been met using recent technical improvements such as increasing magnetic field strength, dedicated sequences (such as double-inversion preparation pulses to suppress the signal of flowing blood), and navigator techniques to correct for respiratory motion.

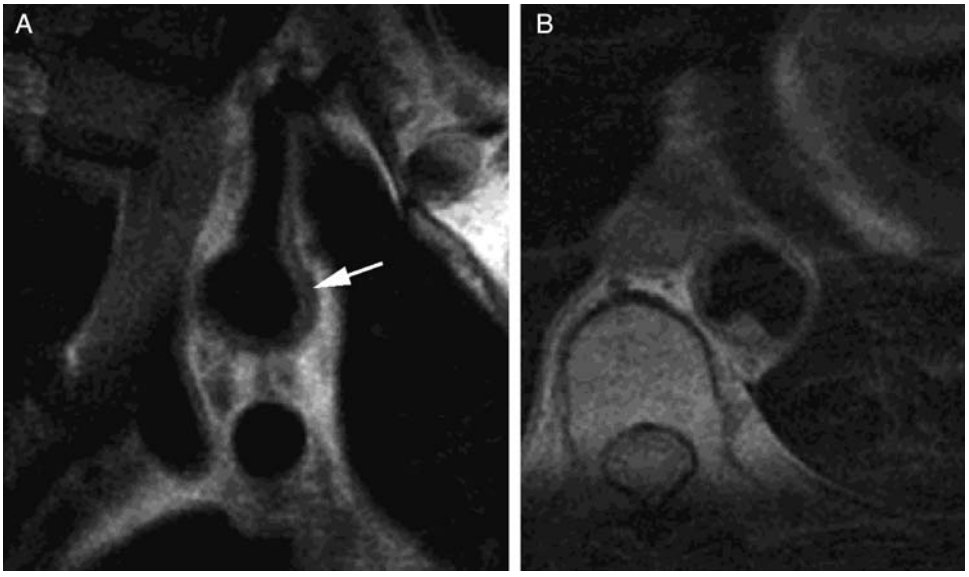

Figure 6 Magnetic resonance imaging high-resolution T2W oblique imaging of the aortic arch demonstrating an atherosclerotic plaque particularly evident in the posterior wall (arrow) extending in the left subclavian artery (*A*). (*B*) A protruding 4 mm thick plaque at the level of the distal thoracic aorta.

Increased wall thickness of the ascending aorta was demonstrated in patients with homozygous familial hypercholesterolaemia (*Figure 6*).[52] The use of contrast enhancement with gadolinium-DTPA aids in the differentiation of plaque components in abdominal aortic aneurysm.[36] In asymptomatic subjects followed in the Framingham Heart Study (FHS), MRI was used to assess the prevalence and extent of atherosclerotic disease. Plaque burden significantly increased with age and was higher in the abdominal aorta than in the thoracic aorta.[53] It was also found that long-term measures of risk factors and FHS coronary risk score are strongly associated with asymptomatic aortic atherosclerosis as detected by MR.[54] Another study showed an association between the distribution of aortic atherosclerosis and both the presence of cardiovascular risk factors and coronary artery disease in patients referred for coronary angiography.[55] It was also highlighted that the thoracic and abdominal aorta might have different susceptibilities to risk factors.

Wentzel *et al.*[56] reported the association between plaque distribution and size and average low shear stress locations. The data support the role of local haemodynamic conditions in the development of atherosclerotic lesions in descending thoracic aorta (*Figure 7*).

Assessment of peripheral artery plaques

High-resolution MR plaque imaging of the femoral and popliteal artery and the response to balloon angioplasty have been recently reported.[20,21] Coulden *et al.*[21] identified atherosclerotic lesions with cross-sectional areas ranging from 49 to 76% of the potential lumen area even in angiographically 'normal' vessel segments. Following percutaneous transluminal angioplasty (PTA), plaque fissuring and local dissection have been easily identified by MRI, and serial changes in lumen diameter, blood flow, and lesion size can be documented. Corti *et al.*[20] showed that cross-sectional high-resolution MRI performed 24 h after PTA at the level of the arterial occlusion revealed severe disruption and splitting of the atherosclerotic plaque, resulting in an irregular-shaped lumen (*Figure 8*). Angiographic and MR images were clearly discrepant, with angiography underestimating the residual lesion. This observation provided *in vivo* evidence of extensive plaque disruption induced by balloon angioplasty and may explain mechanisms of potential complications of this invasive treatment. More recently, Wyttenbach *et al.*[57] reported the effects of PTA and endovascular brachytherapy on vascular remodelling of human femoropopliteal artery by non-invasive MRI. Therefore, cross-sectional analysis by MRI could be useful in follow-up to define plaque remodelling and, perhaps, to identify prognostic factors for restenosis (e.g. plaque splitting).

Assessment of coronary atherosclerosis

Obviously, the ultimate goal would be non-invasive imaging of coronary artery plaque. After preliminary studies in the pig model,[22,28] high-resolution black-blood MRI of both normal and atherosclerotic human coronary arteries was performed. Fayad *et al.*[23] were the first to demonstrate the feasibility of coronary plaque imaging in humans *in vivo*. Coronary MR plaque imaging was performed during breath holding in order to minimize respiratory motion. This technique was subsequently improved by Botnar *et al.*,[58] allowing for high-resolution coronary plaque imaging during free

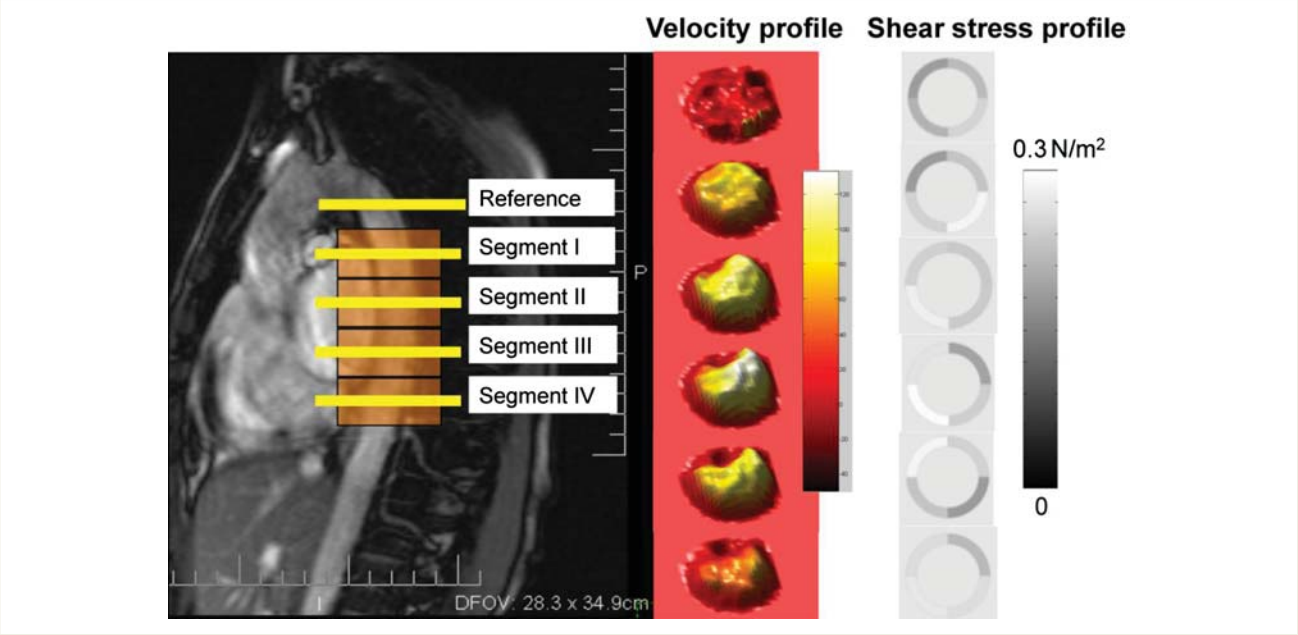

Figure 7 Velocity profiles at different levels of the descending aorta (left panel) can be measured by magnetic resonance imaging and used to derive shear stress. The middle panel show the velocity spectral analysis for the different segment and the right panel indicates the related shear stress condition as described by Wentzel *et al.*[56]

breathing. To alleviate the need for breath holding, the black-blood fast-spin echo method has been combined with a real-time navigator for respiratory gating and real-time slice-position correction.[58–60] Near isotropic spatial-resolution black-blood imaging may provide a quick way to image a long segment of the coronary artery wall and may be useful for rapid coronary plaque burden assessment.[61] Further improvement in external coils, as well as the use of contrast agents that enhance the different vessel wall components, may improve MR characterization of the high-risk plaque in the coronary arteries.

Multimodality and molecular imaging

The combination of different modalities allows useful synergies for non-invasive *in vivo* imaging. This approach was used to investigate plaque neovascularization and inflammation in experimental atherosclerosis *in vivo* by combining contrast-enhanced MRI and PET at the level of the atherosclerotic aorta.[62] Fusion technology to combine different imaging approaches was also tested in humans at the level of the carotid arteries (*Figure 9*).

Of particular interest is the development of novel molecular enhancers that allow the targeted imaging of cells, molecules, and biological processes.[15] Such an approach most likely will allow a more detailed characterization of the biological properties of atherosclerotic plaques, which up to now is not possible *in vivo*. Molecular targets for fibrin, macrophages, and high-density lipoprotein (HDL) have been tested at the pre-clinical level to visualize thrombotic material, inflammation, or transport of HDL metabolism within atherosclerotic plaques *in vivo*.[63,64] The ability to image the presence or biological activity of specific molecules ('molecular imaging') in atherosclerotic plaques *in vivo* is of considerable interest. Assessment of molecular information *in vivo* requires high-affinity, target-specific contrast agents, with marked signal amplification, and high-resolution imaging modalities, such as magnetic resonance. Most of the available paramagnetic magnetic MRI contrast agent constructs, however, are not capable of delivering a large amount of gadolinium ions to induce a large MRI signal. Moreover, some of the MRI contrast agents may be too large to have free access to biochemical epitopes within the vascular subendothelium of atherosclerotic plaques. The role of specific enhancers deserves therefore further investigation.

Magnetic resonance imaging to monitor the effect of an intervention on atherosclerotic lesions

Advances in diagnosis prosper when they march hand-in-hand with advances in treatment. We stand at the threshold of accurate non-invasive assessment of atherosclerosis. Several investigators have recently used serial non-invasive MRI to assess *in vivo* the effects of interventional strategies (such as dietary interventions, systemic medical therapy, or percutaneous balloon treatment) on animal models of arteriosclerosis and in humans.

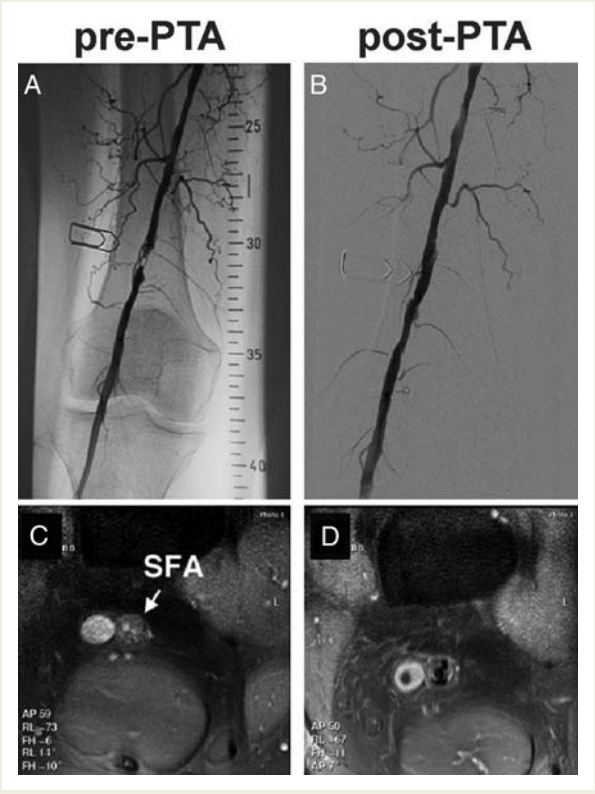

Figure 8 Effect of percutaneous transluminal angioplasty on severe femoral stenosis. Angiography (upper panel) and high-resolution magnetic resonance imaging (lower panel) before and after percutaneous transluminal angioplasty. SFA, superficial femoral artery.

Monitoring of interventions in experimental arteriosclerosis

McConnell *et al.*[65] studied the effects of dietary cholesterol-lowering interventions in rabbits. Arteriosclerosis was induced by a combination of aortic balloon injury and high-cholesterol diet for 4 months. The animals were then assigned to low-cholesterol vs. continued high-cholesterol diet for up to an additional 16 months. Aortic plaque progression was noted in rabbits maintained on a high-cholesterol diet, whereas plaque regression occurred after resuming a low-cholesterol diet. In Watanabe heritable hyperlipidaemic rabbits which lack the LDL receptor, Worthley *et al.*[66] performed serial MRI at baseline and 6 months after aortic balloon denudation and reported that the increase in atherosclerotic plaque burden over time was completely accounted for by positive arterial remodelling. Corti *et al.*[67] reported plaque regression and features of plaque stabilization by a combination of statins and a selective agonist of peroxisomal proliferator-activated receptor gamma (PPARγ-agonist) in the atherosclerotic rabbit. Viles-Gonzalez *et al.*[68] studied the effect of a novel antithrombotic therapy by inhibition of the thromboxane A2 receptor on aortic atherosclerotic lesion in rabbits. They reported regression of advanced atherosclerotic plaques and the reduction in the markers for macrophages, apoptotic cells, metalloproteinases, and endothelin-1 and an increase in vascular smooth muscle cells, suggesting that this thromboxane A2 receptor inhibitor may not only halt the progression of atherosclerosis, but also transform lesions towards a more stable phenotype. They concluded that the possibility of combining antithrombotic and antiatherosclerotic activity by means of the administration of thromboxane A2 receptor inhibitors deserves further investigation in a clinical setting.

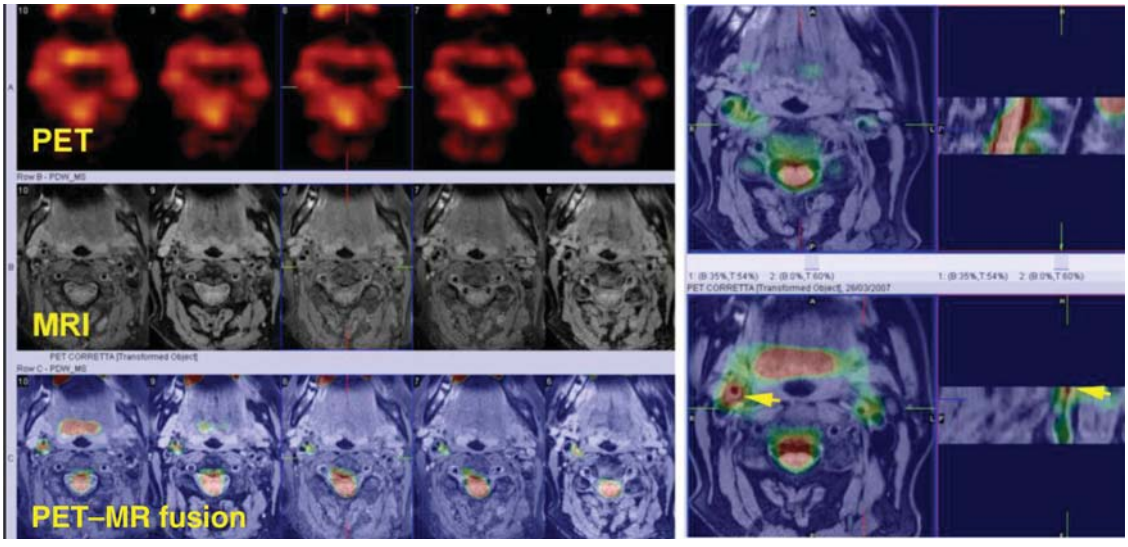

Figure 9 The positron emission tomography–magnetic resonance fusion images of the carotid arteries performed in a patient with acute stroke demonstrate a 'hot spot' (yellow arrow) at the origin of the right internal carotid artery. This could potentially reflect the inflammation (as detected by positron emission tomography) responsible for the rupture of the atherosclerotic plaque (published with the permission of Prof. A. Gallino, Prof. L. Giovanella, and Dr L. Ceriani, Bellinzona, Switzerland).

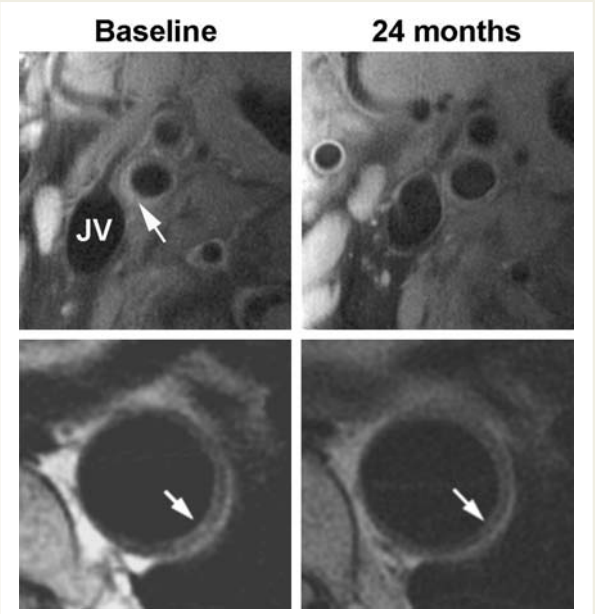

Figure 10 Matched magnetic resonance images of the right carotid bifurcation (upper panels) and the descending aorta (lower panels) in a hypercholesterolaemic patient at baseline and after 24 months of simvastatin therapy. A regression of the plaque (indicated by arrows) with small enlargement of the lumen is evident.[37,69,71] JV, jugular vein.

In vivo monitoring of therapy with magnetic resonance imaging in humans

Effects of lipid-lowering by statin

Corti *et al.*[37] used *in vivo* MRI to quantify the effects of lipid-lowering therapy by statins in asymptomatic previously untreated hypercholesterolemic patients with carotid and aortic atherosclerosis. Atherosclerotic plaques were visualized and measured with MRI at different time points in a longitudinal, uncontrolled study. Significant regression of atherosclerotic lesions was observed. Importantly, despite the early and expected lipid-lowering effect of the statins, a minimum of 12 months was needed to observe significant changes of the vessel wall in early atherosclerotic disease. In a more recent study using a similar design in patients with coronary artery disease (therefore expected to have more advanced disease) significant regression was already seen at 6 months.[38] Corti *et al.* observed a decrease in the VWA but no change in the lumen area at 12 months. A longer follow-up showed a continued reduction in the arterial wall area and even a small, but significant, increase in the arterial lumen at 24 months (*Figure 10*).[69] In the same study population, Wentzel *et al.*[56] showed that shear stress does not seem to be the major predictor for plaque regression by lipid-lowering interventions, suggesting that other mechanisms are involved in the lipid-reversal mechanism.

Lima *et al.*[38] measured atherosclerotic plaques in the thoracic aorta by combined surface and transoesophageal MRI in 27 patients (treated with simvastatin 20–80 mg daily) before and after 6 months of therapy. They confirmed that plaque regression was strongly associated with LDL cholesterol reduction. A *post hoc* analysis of the study by Corti *et al.*[71] revealed that the changes in vessel wall parameters are more related to LDL cholesterol reduction rather than the dose of statin. In fact, no difference in vascular effects was detected between the randomized doses (simvastatin 20 vs. 80 mg). More interestingly, patients reaching mean on-treatment LDL cholesterol $\leq$100 mg/dL showed larger decreases in plaque size compared with patients who did not reach this goal.

In another study, 43 patients with moderate hypercholesterolaemia (LDL cholesterol between 100 and 250 mg/dL) and $<$80% carotid stenosis by duplex ultrasound were randomized to receive either a low (5 mg) or high (40/80 mg) dose of rosuvastatin. The significant reduction in LDL cholesterin levels has paralleled with a reduction in lipid-rich necrotic core size at 24 months. Interestingly, rosuvastatin was associated with a reduction in lipid-rich necrotic core size, whereas the overall plaque burden remained unchanged over the course of 2 years of treatment.

More recently, the ATHEROMA study demonstrated that aggressive lipid lowering with atorvastatin 80 mg daily over a 3-month period was associated with a significant reduction in plaque inflammation measured using ultrasmall superparamagnetic iron oxide particles.[70]

Using the same study design, Yonemura *et al.*[72] investigated the effects of 20 vs. 5 mg atorvastatin on thoracic and abdominal aortic plaques in 40 hypercholesterolaemic Japanese patients who were randomized to receive either dose. They reported that 1-year 20 mg atorvastatin treatment induced regression of thoracic aortic plaques with marked LDL cholesterol reduction, whereas it only retarded plaque progression in the abdominal aorta. Possibly, thoracic and abdominal aortic plaques may have different susceptibilities to lipid lowering. In another remarkable study, Zhao *et al.*[73] examined carotid plaque composition quantitatively by MRI in eight patients with combined hyperlipidaemia who had been treated intensively with lovastatin, niacin, and colestipol for 10 years. An untreated, non-randomized control group was composed of eight patients matched for age and baseline lipoproteins. In the control group, the atherosclerotic lipid core comprised 17% of carotid intima–media cross-sectional area. In the treated group, only 1% of the cross-sectional area belonged to the lipid core ($P = 0.01$ for the comparison). Thus, the lipid core seemed to be almost eliminated from the lesions by metabolic/pharmacological treatment. The 8 treated patients were randomly chosen from a larger group of 60 patients treated intensively, and the larger group experienced only three major coronary events (cardiac death or myocardial infarction) over 10 years, or 0.5% per year.[73]

Taken together, these findings provide evidence that lipid-lowering therapy by statin may have a beneficial effect on plaque volume and composition, by reducing lipid-rich core and local inflammation as assessed by non-invasive MRI. These *in vivo* human studies provide the evidence for previous observations based on histological finding on experimental models of atherosclerosis.

Open issues

Despite rapid improvements of non-invasive imaging techniques such as MRI for the *in vivo* evaluation of atherothrombosis, their application at the clinical level is still hampered by opened issues that require further intensive research (*Table 1*). For instance,

Table 1 Advantages and limitations of non-invasive imaging of atherosclerosis by magnetic resonance imaging

	Advantages	Limitations
Technique	Non-invasive and non-destructive Any exposition to radiation No need for contrast agents Adequate spatial resolution for large vessels (i.e. aorta, carotid, and femoral arteries)	Limited temporal resolution hampering its application in the coronary circulation
Methodology	Adequate for serial imaging Optimal matching of the images over time	Lack of generally accepted protocol for vascular imaging (single vs. multiple sequences)
Validation	Quantitative measurement of vessel wall dimensions Qualitative assessment of plaque composition	Missing a quantitative assessment method for plaque composition and automated operator independent software for the quantitative assessment of plaque dimension and composition

studies are needed to elucidate the inter- and intra-individual variability in the distribution of atherosclerotic plaques, and the ability of non-coronary atherosclerotic plaques imaging to predict cardiovascular events. In fact, most of the data presently available have been obtained in angiographic or autopsy studies. The availability of robust non-invasive techniques to image atherosclerotic vessels will now allow comprehensive studies of atherosclerosis distribution and the correlation between plaque burden and cardiac, cerebrovascular, and peripheral vascular events, respectively. In addition, we are still missing adequate data on the natural course of atherosclerosis. Progression of atherothrombosis is most likely characterized by non-linear growth. At present, the mechanisms of progression remain very speculative. The discussion between balanced infiltration of lipids and inflammatory cells into the intima and media, and healed plaque disruption remain the more accredited.

In addition, at present, it is still unknown whether spontaneous regression of atherosclerotic lesions is also possible in adults and/or in late stages of the disease process. In fact, in young men, regression of early atherosclerotic lesions (such as fatty streaks) appears to be possible. An additional crucial issue is whether the detection of high-risk plaques will enable the prediction of cardiovascular events.

Despite very rapid technical evolution of all non-invasive imaging modalities, their application in the coronary circulation remains limited and mainly hampered by the spatial and temporal resolution.

Actual limitation and future developments of magnetic resonance imaging

The actual limitations of non-invasive imaging of coronary atherosclerosis by MRI are mainly due to technical limitation limiting temporal resolution and hampering therefore its application in rapid moving vessels such as the coronaries. Methodological limitations derived from the lack of generally accepted protocols with standardized sequences for multicontrast imaging limit its application to hospital with MRI physicists able to modify these imaging parameters. In addition, a validated automated operator-independent software for quantitative assessment of plaque dimension and composition is still missing. Finally, the high costs associated with this technique will limit the use of MRI for screening purposes.

Despite these limitations, carotid MRI based on the burgeoning data from prospective studies has placed this technique at the precipice of translation from the established imaging tool dedicated to research purposes only to clinical practice.[74]

Conclusion

The assessment of atherosclerotic burden by imaging techniques appears an essential tool for the identification of high-risk plaques and the risk stratification of the individual patients. The identification of asymptomatic individuals at risk for near-term atherosclerotic events to ensure optimal preventive treatment remains a challenging goal. The BioImage Study[11], as part of the High-risk Plaque (HRP) initiative, is a joint research and development effort whose ultimate objective is to determine cost-effective treatment strategies for individuals at intermediate or high cardiovascular risk and is aiming to evaluate the role of imaging in the assessment of individual cardiovascular risk.[75] Although not yet available for routine use, *in vivo*, high-resolution, multicontrast MRI remains the most promising method of non-invasively imaging plaques and characterizing the main plaque components. Intraplaque haemorrhage and the lipid-rich necrotic core are the best indicators of lesion severity currently visualized by high-resolution MRI. However, MRI methods capable of imaging other important aspects of atherosclerotic disease *in vivo*, including inflammation, neovascularization, and mechanical forces, are emerging and may aid in advancing our understanding of the atherothrombotic disease.[74,75]

Non-invasive MRI also allows serial evaluation of the progression and regression of atherosclerosis over time. Therefore, this technology is particular appealing to test the effects of novel anti-atherosclerotic drugs using plaque morphology as a surrogate endpoint before investing in hard endpoint trials.

Magnetic resonance imaging technology is evolving rapidly and will open up new areas for the diagnosis, prevention, and treatment of atherosclerosis in all arterial locations.

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